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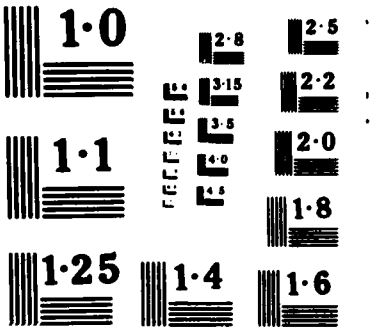
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The overall goal of this research is to provide insights into the adaptive capabilities of individual neurons, which will lead to the development of machines having some of the information processing capabilities of the nervous system. During the period between 01 August 1984 and 31 July 1987, significant progress has been in three major directions. First, experimental studies on the modulation of ionic conductance mechanisms have been performed on individual neurons that are believed to contribute to neuronal plasticity and classical conditioning of defensive reflexes. Second, we have begun to identify elements of the neuronal circuit that contributes to operant conditioning of feeding behavior. Third, a single-cell neuronal model for classical conditioning has been developed and simulated on a digital computer.

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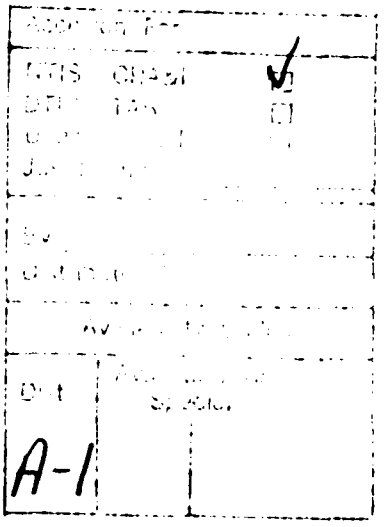
In the experimental studies on classical conditioning, sensory neurons in the marine mollusc Aplysia, which show adaptive capabilities were examined. A neurotransmitter, serotonin, that is released by reinforcing stimuli was found to modulate several different voltage-dependent K^+ conductance mechanisms. These changes affect the excitability of the cell and the duration of action potentials in the sensory neurons and therefore modulate the release of neurotransmitter. In the experimental studies on the neural control of feeding behavior, identified motor neurons, which generate feeding movements were examined and critical command neurons which drive the motor neurons were identified and characterized. In the simulation studies, a single-cell neuronal model for associative learning was developed, which is based on modern cell biological principles. The model accurately simulates available empirical data on synaptic plasticity in the sensory neurons. In addition, it successfully predicts an inter-stimulus-intervals (ISI) function curve that is in good agreement with available behavioral data from Aplysia and other animals, including man.



Final Technical Report

Grant Number: AFOSR-84-0213

Grant Title: Analysis and Synthesis of Adaptive Neural Elements

Period of Report: 1 August 1984 through 31 July 1987

I. Summary

The overall goal of this research is to provide insights into the adaptive capabilities of individual neurons, which will lead to the development of machines having some of the information processing capabilities of the nervous system. During the period between 01 August 1984 and 31 July 1987, significant progress has been in three major directions. First, experimental studies on the modulation of ionic conductance mechanisms have been performed on individual neurons that are believed to contribute to neuronal plasticity and classical conditioning of defensive reflexes. Second, we have begun to identify elements of the neuronal circuit that contributes to operant conditioning of feeding behavior. Third, a single-cell neuronal model for classical conditioning has been developed and simulated on a digital computer.

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II. Research Objectives

The proposed research is designed to examine the adaptive cellular components of a simple biological system that displays basic attributes of intelligence. The objectives are to identify the subcellular processes that underlie the capability of a single neuron for associative information processing, long-term memory, and goal-seeking behavior. Single identified sensory and interneurons in the mollusc Aplysia that have demonstrated capacities for associative conditioning are being investigated. Cellular neurophysiological techniques are being applied to identify the particular ionic conductances and second messenger systems causally involved in adaptive cellular behavior. Formalisms of the subcellular modifications are being developed and incorporated into a quantitative model of the adaptive neural element. The model is being simulated on a digital computer to assess its ability to fit the experimental data and predict features of associative conditioning in other animals (including humans). Similar studies were initiated to examine the neural basis of operant conditioning. As critical loci are identified, the underlying cellular mechanisms will be analyzed.

III. Status of Research (Progress Report)

Progress during the grant has been in three areas. The first deals with experimental studies on modulation of ionic conductance mechanisms in individual neurons that are believed to contribute to neuronal plasticity and classical conditioning. The second deals with experimental studies on the neural basis of operant conditioning. The third focus has been on the development of mathematical models that simulate aspects of associative learning at the single-cell level.

A. Experimental Analysis of Cellular Mechanisms Underlying Learning

Two different neuronal preparations are beer used to investigate the cellular mechanisms underlying learning. First, we have applied voltage-clamp techniques to individual tail sensory neurons to examine the regulation of ionic conductances in response to the type of modulatory inputs that occur during sensitization and classical conditioning of the tail withdrawal reflex. Second, we have identified elements of the neuronal circuit that contributes to operant conditioning of feeding behavior.

1. Modulation of membrane currents in sensory neurons

In the sensory neurons that mediate the tail withdrawal reflex in Aplysia the neurotransmitter serotonin (5-HT) produces a depolarization that is associated with a decrease in their input conductance. This mechanism is thought to contribute to one type of non-associative learning, sensitization and to a simple form of associative learning, classical conditioning. Previous studies have shown that 5-HT increases the levels of cAMP in these cells and that injection of cAMP produces decreases in membrane conductance similar to those produced by 5-HT.

We have utilized the techniques of two-electrode voltage-clamp and computer subtraction in order to examine the current(s) modulated by 5-HT in the tail sensory neurons. Membrane currents were activated by 200 msec duration voltage steps (-30 to 50 mV) from a 25 sec prepulse to -70 mV. Cells were held at the resting potential between steps and the voltage steps were separated by 80 sec. At least 3 responses at each voltage were averaged before and after application of 5-HT (10 to 100 uM).

The isolated current modulated by 5-HT had a complex time- and voltage-dependence. With small depolarizations (up to -10 mV), the isolated 5-HT current appeared to have only one component that was relatively linear with respect to voltage and had a fairly constant time-to-peak of about 130 msec. With greater depolarizations (0 to 50 mV), the isolated current modulated by 5-HT began to include other components that were highly voltage-dependent, including: i) a fast component that peaked at about 20 msec and reflected a significant decrease in the outward current early in the voltage step, and ii) a slower component in steps above 20 mV that reflected an increased outward current. The increased outward current was attenuated by Co^{2+} and Ni^{2+} but was relatively unaffected by low concentrations of

tetraethylammonium (TEA) (0.5, 2 and 5 mM). Both voltage-dependent components were blocked by 100 mM TEA. The 5-HT modulated current remaining in 100 mM TEA was similar to the current modulated at small depolarizations (see above). While other interpretations are possible, the component blocked by 100 mM TEA may represent a slowing of the activation and inactivation kinetics of the delayed K^+ current ($I_{K,V}$) by 5-HT.

The component of 5-HT modulated current remaining in 100 mM TEA has properties consistent with previous descriptions of the S-current (Klein et al, 1982) while the other component (the delayed K^+ current) has not been described previously. Interestingly, the effects of 5-HT on modulating the S-current could by mimicked by application of cAMP, whereas the delayed K^+ component could not. These results indicate that 5-HT may exert its effect on the delayed K^+ current via a second messenger other than cAMP. These results and others (Boyle et al., 1984; Walsh and Byrne, 1985), indicate that the effects of 5-HT on modulating cellular properties of these neurons are rather complex. While complex, all the effects may act synergistically to modify synaptic transmission at the sensory-motor neuron synapse.

The use of the method of computer subtractions has allowed, for the first time, a detail investigation of the serotonin-sensitive membrane currents. The kinetics and voltage-dependence of the responses indicated that the serotonin-modulated currents had several components rather than a single component as was first believed. The magnitude and time-course the second component suggest that this current may play a significant role in modifying the waveform of the action potential. The first, slow current, may be important in regulating cell excitability and cell adaptation to prolonged stimulation. By incorporating these currents into computer simulations of these neurons (see below), will we be able to determine the functional significance of each current.

2. Operant conditioning of feeding behavior

The feeding behavior of Aplysia can be modified by procedures that resemble those giving rise to operant conditioning in higher animals. Previous behavioral studies have indicated that these procedures alter the motor patterns selected by animals when exposed to food. When feeding behavior is paired with negative reinforcement, Aplysia subsequently reject food rather than biting and swallowing it, while pairing of feeding with positive reinforcement increases the likelihood of responding with bites and swallows.

Feeding in Aplysia consists of three motor acts occurring spontaneously, and in response to food: biting, swallowing and rejection. Rejection can also be initiated by peripheral nerve stimulation. Operant conditioning and other forms of plasticity in part are due to selective changes in expression of different motor acts. To begin investigating the neural basis of operant conditioning, we characterized motor patterns expressed by the buccal ganglia, and identified some neurons generating them.

We recorded intracellularly from motor neurons B4 and B5 to monitor activity presumably associated with feeding behavior. In an isolated ganglion preparation, two well-defined patterns of spontaneous rhythmic activity occur. Rhythm #1, seen in about 50% of preparations, is associated with a large compound EPSP. It has a frequency of 1-10 sec, period of 0.5-3 sec, and amplitude of 2-20 mV. Rhythm #2, seen in almost every preparation, is less regular but is composed of three distinct bursts of action potentials, that are superimposed on a sustained depolarization lasting 10-20 sec. Rhythm #2 can also be elicited by stimulation of most buccal nerves, but particularly the radular nerve.

We identified neurons in a number of regions of the buccal ganglion that are prominently active with these rhythms. Of particular significance, however, was the discovery of a group of cells whose activity is closely associated with rhythm #2. These cells fire in synchrony with the activity in the motor neurons. Artificial stimulation of these newly identified group of electrically coupled cells produced monosynaptic EPSPs in B4 and initiated the complete pattern of rhythm #2. Hyperpolarization of a single cell blocks its own rhythmic activity as well as the rhythmic activity in the motor neurons. Thus, these cells appear to be part of the command and pattern generating network for aspects of feeding behavior.

The data indicate that the buccal ganglion contains pattern generators for two motor rhythms. Both are likely to be due to synchronous activity of a number of cells. Most if not all of the pattern generator for rhythmn #2 has been identified and characterized. Future studies will determine the functional role of these pattern generators, and we will attempt to modify their activity with stimuli simulating those producing operant conditioning. For example, stimulating the various buccal nerves modulates the patterns, by changing their relative likelihood of occurrence, and by modulating their frequency and amplitude. Thus, we will attempt to pair spontaneous activity in the bursting cells with stimuli that simulate reinforcement, such as extracellular stimulation of the esophageal nerves and intracellular depolarization and hyperpolarization of other identified neurons in the buccal and cerebral ganglion. Biophysical and biochemical correlates of plasticity in these cells will be investigated, to determine whether mechanisms giving rise to operant conditioning may be similar to those already demonstrated to contribute to classical conditioning in Aplysia.

B. Simulation of Neuronal Function During Learning

Recently, a novel cellular mechanism, activity-dependent neuromodulation, was identified in sensory neurons mediating the gill and tail withdrawal reflexes in Aplysia. This mechanism may explain associative learning on a behavioral level. We mathematically modeled subcellular events that may underlie this mechanism and examined the ability of the model to fit available empirical data. In this associative model, the reinforcing or unconditioned stimulus (US) leads to nonspecific enhancement of transmitter release from sensory neurons by activating a cAMP cascade. Spike activity in sensory neurons, the conditioned stimulus (CS), transiently elevates intracellular Ca^{2+}. The CS-triggered increases of intracellular Ca^{2+} 'primes' the cyclase

and amplifies the US-mediated cAMP synthesis. As a result of pairing specific amplification of cAMP levels, transmitter release is enhanced beyond that produced by unpaired stimuli or by application of the US alone. The model is capable of fitting empirical data on activity-dependent neuromodulation and predicts a characteristic interstimulus interval (ISI) curve. At the subcellular level, the model's ISI function is related to the time-course of the buffering of intracellular Ca^{2+}. The magnitude and duration of the pairing specific enhancement of transmitter release is related to the levels and time-course of intracellular cAMP stimulation.

By incorporating information obtained from recent cellular studies in Aplysia and emerging cell biological principles and mechanisms in other systems this model demonstrates that the same subcellular mechanisms contributing to non-associative learning (sensitization) can be utilized through the addition of a single biochemical step (Ca^{2+}-modulation of adenylate cyclase) to produce an associative neuronal mechanisms that may contribute to associative learning Aplysia. The generality of this mechanism needs to be determined and it would be premature to say that it is the only mechanisms contributing to associative learning. Its intrinsic simplicity is appealing however, since at the subcellular level the formation of associations is dependent upon an interaction of two well-established intracellular second messengers, Ca^{2+} and cAMP.

While the model is capable of predicting some features of associative learning, it cannot predict aspects of associative learning that depend upon an interplay of more than one stimulus to different sites, or more than one stimulus modality. This is so simply because the model is based on a single neuron. By incorporating the present model into a circuit that includes multiple sensory neurons as well as modulatory or facilitatory interneurons, however it will be possible to test its ability to predict more complex features of associative learning.

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15. Susswein, A.J. and Byrne, J.H. Identification and characterization of neurons initiating patterned neural activity in the buccal ganglion of Aplysia, submitted for publication.

16. Baxter, D.A. and Byrne, J.H. Analysis of two K^+-currents modulated by serotonin in the pleural sensory neurons of Aplysia, submitted for publication.

V. Professional Personnel

Baxter, Douglas, Ph.D.
Byrne, John, Ph.D.
Gingrich, Kevin, M.D.
Susswein, Abraham, Ph.D.

VI. Interactions

Aspects of the work were presented at the previous three Society for Neuroscience meetings and two abstracts will be presented at the Society for Neuroscience meeting in Washington, D.C. this November. The work was also presented at the Conference on Neuronal Plasticity: Theoretical and Empirical Approaches, which was held in Woods Hole, Massachusetts, on April 29 to May 1, 1987.

VII. New Discoveries and Specific Applications

The most notable achievements were the discovery of novel outward currents modulated by serotonin and the development of a single-cell neuronal model for associative learning. It is too early in the research to comment on specific applications of this research but eventually the results will be relevent to aspects of artificial intelligence. No inventions were made.

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